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A General Synthesis of Substituted Formylpyrroles from Ketones and 4-Formyloxazole

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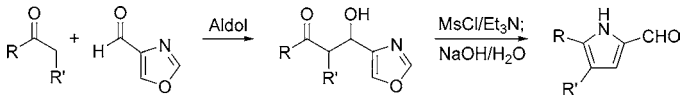
ABSTRACT



A novel two-step synthesis of substituted 2-formylpyrroles is described. Aldol adducts of ketones and 4-formyloxazole undergo a dehydration/oxazole hydrolysis/cyclization cascade on sequential treatment with MsCl/Et_3N and aqueous NaOH to yield 5-substituted and 4,5-disubstituted 2-formylpyrroles. The methodology was extended to an *N*-benzyl thiazolium salt.

Substituted 2-formylpyrroles are useful intermediates in the preparation of heterocyclic scaffolds such as 6-azaindoles,[1] pyrrolo[1,2-*a*]pyrazines,[2] and pyrrolizin-3-ones.[3] Recently we required a practical synthesis of 5-substituted and 4,5-disubstituted 2-formylpyrroles. Herein we describe a simple two-step protocol for annulation of the 2-formylpyrrole moiety onto a variety of ketones.

In pioneering work on the synthesis and reactivity of oxazoles, Cornforth and co-workers reported that various 2-substituted 4-formyloxazoles underwent alkaline hydrolysis to give *N*-acylated aminomalondialdehydes.[4,5] We reasoned that a *vinylogous extension* of Cornforth's reaction may be applicable to the synthesis of 2-formylpyrroles (Figure 1). Initial hydrolytic attack at C_2 of the oxazole ring of enone **A** would lead to an *N*-formyl intermediate, and unlike Cornforth's *N*-acylated substrates, the *N*-formyl group should be cleaved readily under the reaction conditions to give **B** (or an equivalent tautomer). Cyclization of the free amino group onto the pendant ketone (following isomerization to the appropriate olefin geometry) would afford 2-formylpyrrole **C** after dehydration and tautomerization.

To test the feasibility of the reaction, β-(4-oxazolyl)enone **3** was prepared (Scheme 1). Partial reduction of commercially

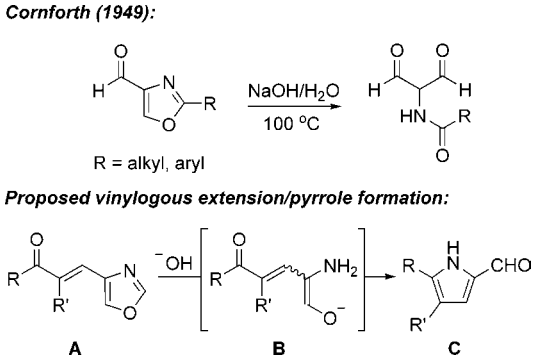


Figure 1. Cornforth's acylaminomalondialdehyde synthesis and our proposed vinylogous extension for pyrrole formation.

(1) Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 8139−8146.
(2) Herz, W.; Tocker, S. *J. Am. Chem. Soc.* **1955**, *77*, 6355−6357.
(3) Campbell, S. E.; Comer, M. C.; Derbyshire, P. A.; Despinoy, X. L. M.; McNab, H.; Morrison, R.; Sommerville, C. C.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2195−2202.
(4) Cornforth, J. W.; Fawaz, E.; Goldsworthy, L. J.; Robinson, R. *J. Chem. Soc.* **1949**, 1549−1553.
(5) For reviews on the chemistry of oxazoles, see: (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389−437. (b) Wiley, R. H. *Chem. Rev.* **1945**, *37*, 401−442.

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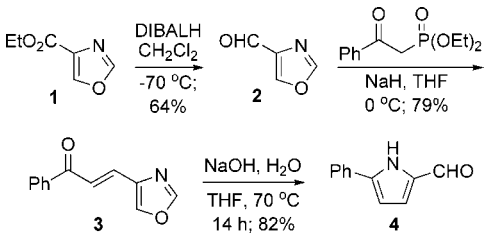
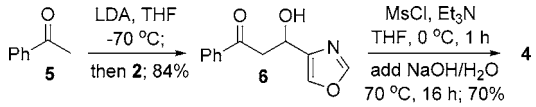
Scheme 1. Synthesis of 4-Formyloxazole (**2**) and Hydrolytic Conversion of β-(4-Oxazolyl)enone **3** to Formylpyrrole **4**



available ethyl 4-oxazolecarboxylate (**1**) with DIBALH gave 4-formyloxazole (**2**) in 64% yield after recrystallization.[6] Horner−Wadsworth−Emmons olefination of **2** with diethyl (2-oxo-2-phenylethyl)phosphonate gave **3** in 79% yield as a single *E* olefin isomer.[7] Gratifyingly, heating **3** in aqueous 2 N NaOH/THF at 70 °C for 14 h produced the desired formylpyrrole **4** in 82% yield.[8]

Although Horner−Wadsworth−Emmons olefination of **2** represents a convenient route to β-(4-oxazolyl)enones, the number of commercially available β-ketophosphonates (or analogous Wittig reagents) is limited. These reagents may be prepared from commercial materials in one or two steps, but we sought a more direct route.[9] Aldol reaction of ketones with **2** would give β-hydroxy-β-(4-oxazolyl)ketones, which on dehydration would provide β-(4-oxazolyl)enones.[10] This aldol/dehydration strategy proved to be viable, and the dehydration and oxazole hydrolysis steps could conveniently be performed in the same pot. Thus, reaction of the lithium enolate of acetophenone **5** (1.1 equiv of LDA, THF, −70 °C, 30 min) with **2** gave aldol **6** in 84% yield (Scheme 2).[11]

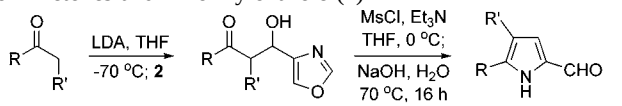
Scheme 2. One-Pot Conversion of Aldol **6** to Formylpyrrole **4**

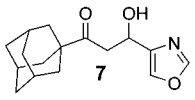
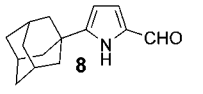
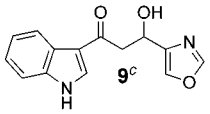
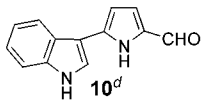
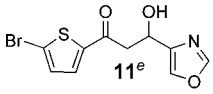
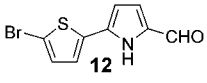
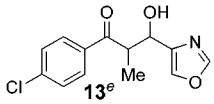
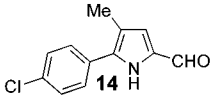
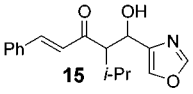
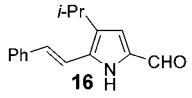
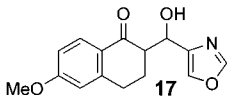
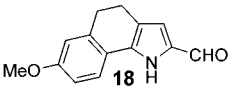
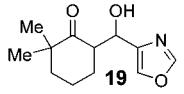
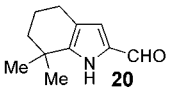
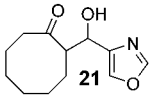
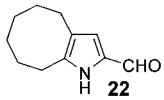
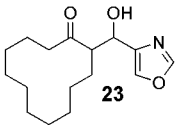
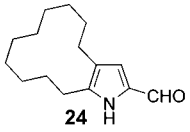


After some optimization, it was found that treatment of **6** with MsCl (1.5 equiv) and Et_3N (3.0 equiv) in THF at 0 °C for 1 h followed by addition of aqueous 2 N NaOH and heating at 70 °C for 16 h gave **4** in 70% yield. It was necessary only to achieve complete mesylation of the aldol prior to addition of aqueous NaOH. The subsequent elimination to give the β-(4-oxazolyl)enones is fast (typically <0.5 h) after addition of aqueous NaOH, whereas with Et_3N in THF this elimination required >24 h at room temperature to reach completion.[12]

Having developed optimized conditions for a two-step synthesis of the required substituted 2-formylpyrroles from ketones and **2**, we explored the substrate scope of the process (Table 1). Aldol reaction of methyl ketones (entries 1−3) with **2** and subsequent dehydration/pyrrole formation gave

Table 1. Two-Step Synthesis of Substituted 2-Formylpyrroles from Ketones and 4-Formyloxazole (**2**)



entry	aldol	yield (%)[a] (dr)[b]	pyrrole	yield (%)[a]
1	 **7**	74	 **8**	72
2	 **9**[c]	68	 **10**[d]	42
3	 **11**[e]	61	 **12**	52
4	 **13**[e]	74[f] (1:1)	 **14**	60
5	 **15**	61[g] (2.7:1)	 **16**	63
6	 **17**	81[f] (1.4:1)	 **18**	61
7	 **19**	67[g] (10.2:1)	 **20**	55
8	 **21**	61[g] (3.7:1)	 **22**	69
9	 **23**	78[f] (1.2:1)	 **24**	64

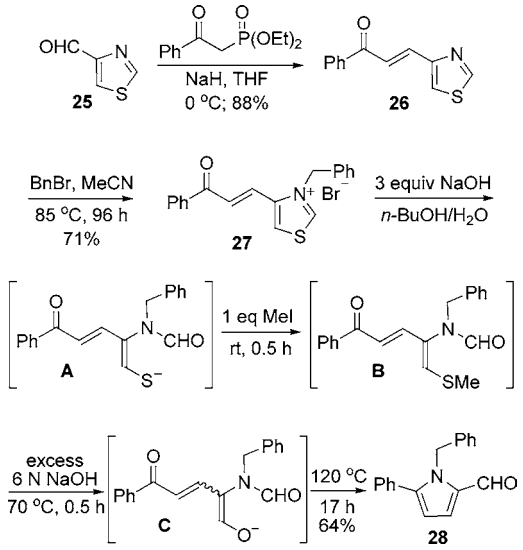
[a] Isolated yield. [b] Diastereomeric ratio determined from ^{1}H NMR of crude product. [c] 2.2 equiv of LDA used in aldol reaction. [d] Hydrolysis time of 48 h. [e] LHMDS (1.1 equiv) used instead of LDA. [f] The mixture of diastereomers was purified by chromatography on SiO_2 and used as such in the next step. [g] The major diastereomer was crystallized from the crude product mixture and used as such in the next step.

(6) For a previous synthesis of 4-formyloxazole, see: Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449−452.
(7) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.
(8) For a previous synthesis of **4**, see: Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, *97*, 4682−4691.
(9) (a) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556−5560. (b) Kim, D. Y.; Kong, M. S.; Kim, T. H. *Synth. Commun.* **1996**, *26*, 2487−2496.
(10) A synthesis of *N*-Boc-2-benzyl-4,5-disubstituted pyrroles by aldol reaction of cyclic ketones with *N*-Boc-L-phenylalaninal and subsequent acid-catalyzed cyclization has been reported: Konieczny, M. T.; Cushman, M. *Tetrahedron Lett.* **1992**, *33*, 6939−6940.
(11) (a) Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459−3460. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn. J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1081.

5-substituted 2-formylpyrroles, while the reaction of higher ketones (entries 4−9) gave 4,5-disubstituted 2-formylpyrroles. In the latter cases the intermediate aldol adducts were formed as a mixture of two diastereomers. In some cases (entries 5, 7, and 8) the major diastereomer crystallized from the crude product mixture and was used as a single diastereomer in the subsequent pyrrole-forming reaction. The yield of aldol adduct in these entries is therefore the isolated yield of major diastereomer. For entries 4, 6, and 9, the mixture of diastereomers was purified by chromatography and used as such in the pyrrole-forming reaction. Control experiments indicated no significant difference in reaction rate or purity profile for diastereomeric aldol adducts. The protocol allowed incorporation of alkyl, aryl, and alkenyl functionality on the 2-formylpyrrole core. Halogenated substrates could be prepared (entries 3 and 4), and offer possibilities for further functionalization via cross-coupling reactions.[13] An N-unprotected indole could be incorporated (entry 2). In this case the aldol reaction was performed via the dianion of 3-acetylindole.[14] Hydrolysis of the resultant aldol **9** was unusually slow (48 h at 70 °C), possibly due to resonance contributions from the partially deprotonated indole nitrogen to the ketone carbonyl attenuating the inductive electron withdrawl from the oxazole ring. The use of cyclic ketones generated bicyclic and tricyclic formylpyrroles (entries 6−9) in good yields.

Extension of the methodology to a β-(4-thiazolyl)enone was explored. These substrates, if they followed the same reaction pathway as the corresponding oxazole systems, could give 2-thioformylpyrroles. In contrast to other thioaldehydes, 2-thioformylpyrroles are known to be fairly stable as a result of electron donation of the pyrrole ring into the C═S double bond, and their formation using this chemistry appeared feasible.[15] Olefination of commercially available 4-formylthiazole **25** gave the requisite enone **26** as a single (*E*)-alkene isomer (Scheme 3). Prolonged exposure of **26** to aqueous NaOH at temperatures up to 120 °C, however, gave primarily recovered starting material and no thioformylpyrrole or formylpyrrole products.[16] It is known that *N*-alkyl thiazolium salts such as thiamine are readily attacked by hydroxide at C_2 to give *N*-formyl enethiolates.[17] We suspected that activation of our system as an *N*-alkyl thiazolium salt could lead, after hydrolysis of the *N*-formyl group, to the corresponding *N*-alkyl 2-thioformylpyrrole. *N*-Benzylation of **26** proceeded slowly but smoothly to give thiazolium

Scheme 3. Synthesis and Hydrolysis of Thiazolium Salt **27**



salt **27** in 71% yield (Scheme 3). Treatment of **27** with excess aqueous NaOH at temperatures up to 120 °C gave small amounts (<5%) of *N*-benzyl 2-formylpyrrole **28** along with a complex mixture of unidentified products. We suspected that the intermediate enethiolate **A** may be unstable under the reaction conditions. *S*-Methylation of **A** would give an intermediate sulfide **B**, which could undergo hydroxide addition/methylthiolate elimination to give intermediate **C**, which in turn should lead to *N*-benzyl pyrrole **28** after hydrolysis of the *N*-formyl group in analogy with the oxazole-based substrates. Exposure of **27** to 3 equiv of NaOH and 1 equiv of MeI at room temperature quickly gave the *S*-methylated intermediate **B** as detected by LC-MS analysis.[18] Subsequent addition of excess 6 N NaOH and heating at 70 °C for 0.5 h completely converted **B** to an intermediate corresponding to **C** by LC-MS analysis, formed as a 2:1 mixture of isomers. Further heating at 120 °C for 17 h effected cleavage of the *N*-formyl group and cyclization to give *N*-benzyl pyrrole **28** in 64% yield.

In conclusion, we have described a unique two-step methodology for the synthesis of 5-monosubstituted and 4,5-disubstituted 2-formylpyrroles. The use of readily available starting materials and reagents and the operationally simple reaction conditions make this an attractive route for assembling structurally diverse 2-formylpyrroles. Although this report makes use of the aldol reaction of lithium enolates with 4-formyloxazole (**2**) for incorporation of the oxazole moiety, in principle numerous alternative aldol reaction conditions may be employed. In addition, the direct olefination of **2** with ketone-derived olefination reagents represents an alternative strategy for accessing the hydrolysis precursors.[19] Although application of the methodology to direct

(12) Attempts to effect direct conversion of **6** to **4** by treatment with aqueous base led primarily to retro-aldol reaction and only traces of **4**.

(13) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vols. 1 and 2.

(14) Byers, J. H.; Zhang, Y. *Heterocycles* **2002**, *57*, 1293−1297.

(15) (a) Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. F.; Ito, S.; Langemann, A.; Le Goff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Volz, H. *J. Am. Chem. Soc.* **1960**, *82*, 3800−3802. (b) Wilton-Ely, J. D. E. T.; Pogorzelec, P. J.; Honarkhah, S. J.; Reid, D. H.; Tocher, D. A. *Organometallics* **2005**, *24*, 2862−2874.

(16) Hydrolysis of thioaldehydes to aldehydes: Muraoka, M.; Yamamoto, T.; Enomoto, K.; Takeshima, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1241−1252.

(17) (a) El Hage Chahine, J.-M.; DuBois, J.-E. *J. Am. Chem. Soc.* **1983**, *105*, 2335−2340. (b) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1991**, *113*, 985−990.

(18) For an example of *N*-alkyl thiazolium hydrolysis/intramolecular *S*-alkylation, see: Federsel, H.-J.; Glasare, G.; Högström, C.; Weistal, J.; Zinko, B.; Ödman, C. *J. Org. Chem.* **1995**, *60*, 2597−2606.

(19) Korotchenko, V. N.; Nenajdenko, V. G.; Balenkova, E. S.; Shastin, A. V. *Russ. Chem. Rev.* **2004**, *73*, 957−989.

hydrolysis of thiazole or *N*-benzyl thiazolium substrates failed to give the desired thioformylpyrrole, *S*-methylation of an intermediate enethiolate allowed the synthesis of an *N*-benzyl 2-formylpyrrole. This methodology should prove useful for the synthesis of pharmaceutical intermediates and natural products.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for **2**−**4**, **6**−**24**, and **26**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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